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CLASSIC ESSENTIAL TREMOR CHANGES FOLLOWING CEREBELLAR HEMORRHAGE

Diagnosis of essential tremor (ET) is based on clinical features.¹ Presence of postural tremor (PT) is a requirement for the diagnosis of classic ET.¹ Kinetic/intention tremor is present in most and resting tremor is seen in some patients with ET.¹ The pathophysiology of ET remains unknown. One recent study reported significant cerebellar Purkinje cell (PC) loss in most ET cases and one autopsied patient revealed marked dentate nucleus neuronal loss.² Since there is no suitable animal model of ET, observations in human subjects are critical to determine the pathophysiology of this disorder. The aim of this case report is to demonstrate transformation of classic ET to cerebellar ataxia and larger amplitude kinetic tremor but resolution of PT following ipsilateral cerebellar hemorrhage.

Case report. A right-handed retired laboratory technologist with hypertension developed bilateral upper limb action tremor at age 30 years. The tremor progressed slowly but required no treatment. Family history revealed that her father had upper limb tremor and her 42-year-old daughter had ET onset at age 30 years. At age 65 she had spontaneous left cerebellar hemorrhage. Computerized tomography revealed a 4.8 × 4.8 left cerebellar hemorrhage (figure). The hematoma was evacuated surgically. Following that, she had marked incoordination and worsening of kinetic tremor in the left upper limb such that she could not use it for daily activities. By age 71, the right upper limb tremor progressed to the point that it was interfering with feeding and drinking. Examination revealed moderate amplitude postural and kinetic tremor and intermittent rest tremor in the right upper limb. In the left upper limb, there was no postural or resting tremor but there was pronounced ataxia and large amplitude kinetic tremor. A video (on the *Neurology*[®] Web site at www.neurology.org) made at age 71 shows marked difference in the tremor characteristics between the right and the left side when same activity is performed separately or simultaneously. There was severe ataxia in the left upper limb and mild ataxia in the left lower limb.

Figure

CT of the brain at age 65 revealed 4.8 × 4.8 cm left cerebellar hemorrhage which extended slightly to the right of midline

She had no nystagmus, head tremor, or motor or sensory deficit on either side.

Discussion. The pathophysiology of ET has not been fully established but clinical, physiologic,³ and imaging studies⁴ suggest cerebellar dysfunction as the basis.

Our patient had classic ET. After spontaneous localized left cerebellar hemorrhage the ipsilateral postural tremor component of ET resolved but she developed marked cerebellar ataxia and large amplitude kinetic tremor. PT is the cardinal feature of classic ET,¹ which in our patient resolved after localized cerebellar hemorrhage. Similar observation was reported after an ischemic stroke in one ET case.⁵ These findings indicate that lesions which involve all components of the cerebellum do not produce classic ET, but manifest as cerebellar ataxia and kinetic/intention tremor.

Recent pathologic studies have reported depletion of cerebellar dentate nucleus neurons and one large study noted that 76% of the ET cases had PC loss and its pathologic sequelae² compared to the normal

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control brains. There was no other brain pathology in these cases.²

Most cerebellar disorders seen in clinical practice where the PC loss is evident also manifest pathology elsewhere in the nervous system. Therefore the role of PC loss alone in the production of tremor is uncertain. Selective severe PC loss was reported in one autopsy case with anti-glutamic acid decarboxylase antibody,⁶ and in one patient with anti-Yo antibody with ovarian cancer.⁷ These cases also manifested proliferation of Bergmann glia in the cerebellum.^{6,7} Both these patients had severe cerebellar ataxia, but there is no mention of tremor. It is possible that the kinetic tremor was masked by ataxia and the postural tremor was not carefully looked for. Thus the definite role of cerebellar Purkinje cell loss in the pathophysiology of classic ET remains to be established. More focused studies are needed to answer that question.

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Supported by PW Golf Classic and Curling Classic.

Disclosure: The authors report no disclosures.

Received March 24, 2008. Accepted in final form June 23, 2008.

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NEONATAL HYPOTONIA CAN BE A SODIUM CHANNELOPATHY: RECOGNITION OF A NEW PHENOTYPE

A 23-year-old French woman had an uncomplicated labor producing a male infant by vaginal delivery (case 4-2 in the table). The initial Apgar score was 10 but very rapidly he developed generalized hypotonia with impaired suckling. Respiration was initially uncompromised. Full blood count, electrolyte profile, C-reactive protein, and blood glucose were all within normal limits. Nasogastric feeding was initiated and the infant was transferred to the pediatric neurology service.

Examination on the first day found the child to be difficult to wake. Major generalized hypotonia was confirmed with only slight movement of the limbs to stimulation. Reflexes were reduced. Systemic examination was unremarkable. From the second day frequent oxygen desaturations were recorded during sleep and he required nasal oxygen therapy for 5 days. A chest x-ray was normal. Over the following week gradual spontaneous improvement occurred. On day 8 examination was normal and no further respiratory or nutritional support was required.

The infant's older brother born 3 years earlier also had transient generalized hypotonia with suckling difficulties but with full recovery. At the age of 3 he began to suffer episodes of muscle paralysis triggered

by cold. The mother of the two children had also had cold exacerbated episodes of muscle stiffness (confirmed to be myotonia on EMG) and paralysis from the age of 4. Her father, grandmother, and great-grandmother experienced similar episodes.

Direct DNA sequencing confirmed the presence of the missense I693T mutation in the domain II S4–5 cytoplasmic loop of the alpha subunit of the voltage-gated skeletal muscle sodium channel (Nav1.4) in affected members of this family including both cases with neonatal hypotonia. This mutation has been reported and validated as a paramyotonia congenita mutation.¹

We have also identified the I693T sodium channel mutation in four additional cases of neonatal hypotonia with or without feeding and respiratory symptoms. These four cases are from two unrelated English families and siblings from one French family (family 3). The table outlines the clinical findings in each case. Earlier generations in families 1, 3, and 4 reported a history of paramyotonia congenita but not of neonatal hypotonia.

Discussion. Paramyotonia congenita is a skeletal muscle disorder caused by impaired inactivation of the voltage gated sodium channel Nav1.4. The inactivation defect results in a hyperexcitable muscle fiber

Table Features of hypotonia and motor development in six neonates carrying the Nav1.4 I693T mutation (the case reported in detail in this case report is 4-2)							
	Sex	Apgar at birth	Onset of hypotonia	Impairment of sucking-swallowing	Desaturation	Kalemia (mmol/L)	Motor development
Family 1 (English)	Female 1-1	NA	Birth	Day 1, bottle fed, unable to breastfeed	No	NA	Walking delayed (19/12)
Family 2 (English)	Female 2-1	NA	Birth	No (hypotonia limited to limbs)	No	NA	Walking delayed (22/12)
Family 3 (French)	Female 3-1	10	Day 1, some hours after birth	Day 1-3, some hours after birth, nasogastric tube	Day 1, some hours after birth (cyanosis); no reported treatment	5.1, then normal	Normal
	Male 3-2	10	Day 1, some hours after birth when bathed	Day 1-3, onset in bath	No	Normal	NA
Family 4 (French)	Male 4-1	NA	Day 1	Day 1-3, no treatment reported	No	NA	Normal
	Male 4-2	10	Day 1, some hours after birth	Day 1-6, some hours after birth, nasogastric tube	Day 2-6, nasal oxygen required	Normal	NA

Following recovery, episodes of cold exacerbated myotonia or paralysis subsequently began in all children before the age of 5 except case 4-2, who has not yet manifest any such symptoms but is currently only 1 year of age.
 NA = not available.

membrane such that a single nerve impulse produces a sequential train of action potentials. This is reflected clinically as myotonia (delayed muscle relaxation following forceful contraction), which usually presents in the first decade and is exacerbated by cold and exercise.² Most commonly the muscles of the face and upper limbs are affected but there are reports of respiratory compromise.³ Patients also commonly experience episodic muscle weakness that can last for hours or even days. Neonatal paramyotonia congenita often presents with myotonic phenomenon when the infant cries or is washed, especially with cool water.⁴ Recently, a rare lethal neonatal paramyotonia case with extreme sensitivity to cold was reported and attributed to another mutation (N1297K).⁵ However, neonatal hypotonia has not previously been reported as a clinical manifestation of muscle sodium channel dysfunction. Our observations in these six individuals from four unrelated French and English families indicate that neonatal hypotonia can be a manifestation of muscle sodium channel dysfunction. The systematic collection of genetic and clinical information in databases at our two centers allowed us to retrospectively identify neonatal hypotonia as a phenotype that was common to individuals with the I693T sodium channel mutation.

Pathologic muscle hypotonia is an important neonatal presentation and can be a sign of either a peripheral or central abnormality. Careful diagnostic assessment and often multiple investigations are required.⁶ Recognition of a sodium channel mutation as a cause of neonatal hypotonia may prevent unnecessary and invasive investigations. For example, a

muscle biopsy is very unlikely to be contributory. EMG assessment has been shown to be beneficial in adults if performed according to specific protocols but these are not easily applicable in neonates.⁷ Treatment in our cases was supportive as symptoms are self-limiting but it is important to recognize that symptoms may be cold-triggered and temperature-dependent. Therefore, a constant warm ambient temperature is essential in such cases.

We conclude that sodium channel gene mutations can cause neonatal hypotonia and that women harboring such mutations should be considered at risk for having neonates with such hypotonia. In addition, where the father is known to be affected these pregnancies should also be considered at risk. The data we present suggest that a sodium channelopathy should enter the differential diagnosis in unexplained neonatal hypotonia, since a positive family history may not always be evident in muscle channelopathies.

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Professor Hanna's research is supported by the Medical Research Council, England. Professor Fontaine's clinical and research network RESOCANAUX is supported by Agence Nationale de la Recherche and GIS Maladies Rares. E. Matthews is a CINCH-NIH fellow (NIH grant no. 1 U45 RR198442-01). This work was undertaken at University College London Hospitals/University College London, which received a proportion of funding from the Department of Health's National Institute for Health Research Biomedical Research Centres funding scheme.

Disclosure: The authors report no disclosures.

Received March 26, 2008. Accepted in final form June 23, 2008.

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LONG-TERM EFFECT OF RITUXIMAB IN ANTI-MAG POLYNEUROPATHY

Recent studies showed that rituximab, a chimeric anti-CD20 monoclonal antibody, reduces antibody levels and ameliorates neuropathy in two thirds of patients with neuropathy and anti-myelin-associated glycoprotein (MAG) monoclonal IgM.^{1–3} Few data are available on the long-term effects of this therapy.⁴ We report on the long-term follow-up of rituximab responders with anti-MAG polyneuropathy.

Methods. Ten patients with anti-MAG polyneuropathy responding to rituximab, 375 mg/sq for four consecutive weekly infusions, were prospectively studied for 36 months. The effects of the initial treatment in 13 patients and the type of assessment were previously described.³ The baseline clinical and laboratory data of the 10 responding patients are reported in the table. All but one patient (no. 1) had an IgM monoclonal gammopathy of undetermined significance and a symptom duration of up to 2 years. Three patients had not been previously treated for the neuropathy, whereas seven were unresponsive to immune or cytostatic therapies. We considered as responders patients who improved at month 12 by at least one point in two clinical scales including MRC sumscore (appendix e-1 on the *Neurology*® Web site at www.neurology.org), INCAT Disability Scale (appendix e-2), and INCAT sensory sumscore (ISS) (appendix e-3). During follow-up, patients underwent clinical, immunologic, and electrophysiologic evaluations every 6 months without additional rituximab infusions, or other therapies. Clinical deterioration was defined as worsening by one point in at least two scales.

Results. All patients improved at 12 months in deambulation with reduction of sensory ataxia in eight and increase in muscle strength in nine, as reflected by improvement in two or more scales (table). Three patients improved also in upper limbs, with improvement of daily activities. Eight patients maintained or ameliorated the clinical improvement through 24 months, when a significant improvement ($p = 0.02$) in both PCS and MCS of the SF-36 was also present (table). Six patients maintained the improvement through the last follow-up at 36-month (table). The four patients deteriorating during follow-up had a slowly progressive increase in sensory ataxia and weakness leading to gait deterioration. No major adverse effects were registered. Anti-MAG titers presented a significant median reduction by 93% at month 12 ($p = 0.005$ vs baseline value), and were still reduced by 80% at month 24 and by ~60% at month 36 ($p = 0.12$ vs baseline value). In eight patients, anti-MAG titers raised during the follow-up, although returning to baseline levels at months 24–36 in only two of them (nos. 9 and 10), and increased by twofold at month 24 in one patient (no. 3) (table). CD19+ B cells were undetectable 1 month after therapy, returned to pretreatment values in eight patients after 12 months, but remained low in two (nos. 5 and 10) throughout the follow-up. Median serum IgM levels remained low by ~60% at month 36 (Wilcoxon test, $p = 0.005$ vs baseline value).

Patients who deteriorated during follow-up were not different from those who did not in term of age, baseline IgM levels, severity and duration of symptoms. All the four patients deteriorating during follow-up had baseline anti-MAG titers $\geq 1/100,000$ (median $\pm$ SE, $100,000 \pm 175,000$),

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Patient (sex, age, y)	IgM levels (mg/dL)				Anti-MAG titers*				MRC				INCAT				ISS				SF-36 PCS				SF-36 MCS			
	T0	T12	T24	T36	T0	T12	T24	T36	T0	T12	T24	T36	T0	T12	T24	T36	T0	T12	T24	T36	T0	T12	T24	T36	T0	T12	T24	T36
1 (M, 48)	200	100*	100	105*	1/100,000	1/12,800*	1/25,600*	1/51,200*	58	60*	60	58*	3	0*	0	3*	7	3*	3	6*	26	40*	29	53*				
2 (M, 66)	600	580*	580	570*	1/800,000	1/25,600*	1/51,200*	1/51,200*	54	56*	50*	50*	4	3*	6*	6	12	12	16*	16	22	24*	29	35*				
3 (F, 64)	300	96*	90*	90	1/100,000	1/25,600*	1/200,000*	1/200,000*	58	59*	59	47*	3	3	2*	4*	11	10*	6*	12*	21	40*	20	50*				
4 (F, 73)	384	175*	153*	149*	1/51,200	1/1,000*	1/3,200*	1/3,200*	58	60*	60	60	2	1*	1	1	8	2*	2	2	22	50*	45	61*				
5 (F, 57)	305	179*	158*	127	1/3,200	1/1,000*	1/1,000*	1/1,000	59	60*	60	60	3	2*	2	2	9	6*	6	6	25	54*	16	60*				
6 (M, 69)	887	394*	359*	362*	1/1,600	<1/1,000*	<1/1,000	1/1,000*	59	60*	60	60	2	1*	1	1	10	5*	5	5	38	50*	44	55*				
7 (M, 70)	284	60*	52*	52	1/3,200	<1/1,000*	<1/1,000	<1/1,000	60	60	60	60	1	0*	0	0	4	2*	2	2	—	—	—	—				
8 (M, 66)	788	550*	500*	289*	1/51,200	1/3,200*	1/6,400*	1/6,400*	46	50*	54*	54	8	7*	4*	4	9	8*	5*	5	—	—	—	—				
9 (M, 82)	186	100*	98*	90*	1/100,000	1/6,400*	1/51,200*	1/51,200*	51	55*	55	55	5	4*	5*	5*	10	10	12*	12	—	—	—	—				
10 (F, 63)	1,250	795*	698*	698	1/51,200	1/25,600*	1/51,200*	1/51,200*	56	59*	59	59	4	2*	2	2	7	6*	6	6	17	27*	37	67*				

Quality of life was evaluated with the Italian version of the Short-Form 36 (SF-36)⁵ in seven patients at baseline, and at 24-month follow-up. Physical Composite Score (PCS) and Mental Composite Score (MCS), related to physical and psychological/emotional distress, were analyzed.
 *Determined by Western blot.³
 MRC = Medical Research Council sumscore (normal, 60; range, 0–60); INCAT = Inflammatory Neuropathy Cause and Treatment arm and leg disability score (normal, 0–10), INCAT Sensory Sumscore (normal, 0; range, 0–20); PCS = Physical Composite Score (range, 0–100); MCS = Mental Composite Score (range, 0–100) (*improvement and †deterioration); T = follow-up expressed in months.

and deterioration coincided with or followed an anti-MAG titers increase. None of the patients maintaining the improvement during the follow-up had baseline titers higher than 1/51,200 (27,200 ± 10,875; Mann-Whitney test, *p* = 0.009) and in only one (no. 10) anti-MAG titer raised to this level during follow-up.

Discussion. Our findings show that a single rituximab course may induce a long-lasting benefit on both clinical and quality-of-life measures in patients with anti-MAG polyneuropathy initially responding to rituximab. These findings agree with studies reporting rituximab sustained efficacy (>24 months) in other autoimmune disorders.^{6,7}

Similarly to what was described,⁶ clinical remissions in our patients lasted despite the reappearance of circulating B cells. Clinical deterioration correlated with high baseline anti-MAG titers, their increase during follow-up, or both. Therefore, anti-MAG titers could help predict not only initial response to rituximab,³ but also clinical follow-up, analogously to what was observed for autoantibodies in pemphigoid gestationis.⁷

Our rituximab responders showed sustained clinical benefits lasting 24 months in 80%, and 36 months in 60%. These findings have relevant clinical implications, since anti-MAG polyneuropathy is a chronic disease requiring long-term treatment, and the high cost of rituximab may be balanced by its long-lasting effects. However, patients with baseline high anti-MAG titers may require additional rituximab courses, both as induction⁴ or maintenance therapy.

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Disclosure: The authors report no disclosures.
Received March 30, 2008. Accepted in final form June 23, 2008.
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